

HETEROCYCLIC KETONE AND THIOESTER COMPOUNDS AND USES

This application is a continuation-in-part of U.S. Patent Application Serial No. 08/904,461, filed August 1, 1997, which is in turn a continuation-in-part of U.S. Patent Application No. 08/721,765, filed September 25, 1996, now U.S. Patent No. 5,786,378, the entire contents of which are considered a part of this application and are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

This invention relates to neurotrophic, low molecular weight, small molecule heterocyclic ketone and thioester compounds, and their use for effecting neuronal activities in animals, including treating neurological disorders.

It has been found that picomolar concentrations of an immunosuppressant, such as FK506 or rapamycin, stimulates neurite outgrowth in PC12 cells and sensory neurons, namely dorsal root ganglion cells (DRGs). Lyons et al., *Proc. of Natl. Acad. Sci.*, 1994, vol. 91, pp. 3191-3195. In whole animal experiments, FK506 has been shown to stimulate nerve regeneration following facial nerve injury and results in functional recovery in animals with sciatic nerve lesions.

Studies have demonstrated that neurodegenerative disorders, such as senile dementia of the Alzheimer's type (SDAT or Alzheimer's disease), Parkinson's disease and amyotrophic lateral sclerosis (ALS), may occur due to the loss, or decreased availability, of a neurotrophic substance specific for a particular population of neurons affected in the disorder. Several neurotrophic factors affecting specific neuronal populations in the central nervous system have been identified.

For example, it has been hypothesized that Alzheimer's disease results from a decrease or loss of

nerve growth factor (NGF). It has thus been proposed to treat SDAT patients with exogenous nerve growth factor or other neurotrophic proteins, such as brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor and neurotrophin-3, to increase the survival of degenerating neuronal populations.

Clinical application of these proteins in various neurological disease states is hampered by difficulties in the delivery and bioavailability of large proteins to nervous system targets. By contrast, immunosuppressant drugs with neurotrophic activity are relatively small and display excellent bioavailability and specificity. However, when administered chronically, immunosuppressants exhibit a number of potentially serious side effects, including nephrotoxicity, such as impairment of glomerular filtration and irreversible interstitial fibrosis (Kopp et al., *J. Am. Soc. Nephrol.*, 1991, 1:162); neurological deficits, such as involuntary tremors, or non-specific cerebral angina, such as non-localized headaches (De Groen et al., *N. Engl. J. Med.*, 1987, 317:861); and vascular hypertension, with complications resulting therefrom (Kahan et al., *N. Engl. J. Med.*, 1989, 321:1725).

To avoid the drawbacks associated with use of large molecule proteins and/or immunosuppressants, the present invention provides small molecule compounds for enhancing neurite outgrowth, and promoting neuronal growth and regeneration in various neuropathological situations where neuronal repair can be facilitated, including: peripheral nerve damage caused by physical injury or disease state such as diabetes; physical damage to the central nervous system (spinal cord and brain); brain damage associated with stroke; and neurological disorders relating to neurodegeneration, such as Parkinson's disease, Huntington's Disease, SDAT

(Alzheimer's disease) and amyotrophic lateral sclerosis (ALS).

SUMMARY OF THE INVENTION

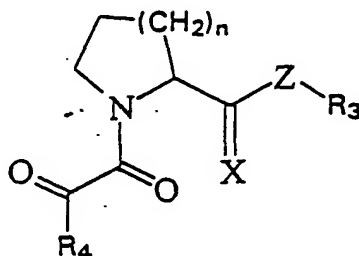
5 The present invention relates to neurotrophic, low molecular weight, small molecule heterocyclic ketone or thioester compounds. In a preferred embodiment, the compounds are non-immunosuppressive. In another preferred embodiment, the compounds of the present
10 invention have an affinity for FKBP-type immunophilins, such as FKBP12; and affinity binding or interaction may inhibit the prolyl-peptidyl *cis-trans* isomerase, or rotamase, activity of the binding protein.

 The present invention also relates to a
15 pharmaceutical composition comprising:

- (i) an effective amount of a neurotrophic, low molecular weight, small molecule heterocyclic ketone or thioester compound; and
- (ii) a pharmaceutically acceptable carrier.

20 The present invention further relates to a method of effecting a neuronal activity in an animal, comprising administering to said animal an effective amount of a neurotrophic, low molecular weight, small molecule heterocyclic ketone or thioester compound.

25 Specifically, the present invention relates to a compound of formula II:



II

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

35 n is 1 or 2;

X is O or S;

Z is selected from the group consisting of S, CH₂, CHR₁, CR₁R₂, and a bond;

5 R₁, R₂, and R₃ are independently selected from the group consisting of C₁-C₃ straight or branched chain alkyl, C₂-C₃ straight or branched chain alkenyl, and Ar, wherein said R₁, R₂, or R₃ is unsubstituted or substituted with one or more halo, trifluoromethyl, nitro, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, hydroxy, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, amino, or Ar;

10 R₄ is selected from the group consisting of C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₃-C₇ cycloalkenyl, and Ar; and

Ar is aryl.

The present invention also relates to a pharmaceutical composition comprising:

- 20 (i) an effective amount of the compound of formula II; and
(ii) a pharmaceutically acceptable carrier.

The present invention further relates to a method of effecting a neuronal activity in an animal, comprising administering to said animal an effective amount of a compound of formula II.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1(A) is a representative photomicrograph of untreated sensory neurons.

30 FIG. 1(B) is a representative photomicrograph of compound 1 (10 pM) promoting neurite outgrowth in sensory neurons.

FIG. 1(C) is a representative photomicrograph of compound 1 (1 nM) promoting neurite outgrowth in sensory neurons.

FIG. 1(D) is a representative photomicrograph of compound 1 (1 μ M) promoting neurite outgrowth in sensory neurons.

5 FIG. 2(A) is a representative photomicrograph of untreated sensory neurons.

FIG. 2(B) is a representative photomicrograph of a related compound, 2-Phenyl-1-ethyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate, (10 pM) promoting neurite outgrowth in sensory neurons.

10 FIG. 2(C) is a representative photomicrograph of a related compound, 2-Phenyl-1-ethyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate, (1 nM) promoting neurite outgrowth in sensory neurons.

15 FIG. 2(D) is a representative photomicrograph of a related compound, 2-Phenyl-1-ethyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate, (100 nM) promoting neurite outgrowth in sensory neurons.

FIG. 3(A) is a representative photomicrograph of untreated sensory neurons.

20 FIG. 3(B) is a representative photomicrograph of a related compound, 2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate, (10 pM) promoting neurite outgrowth in sensory neurons.

25 FIG. 3(C) is a representative photomicrograph of a related compound, 2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate, (1 nM) promoting neurite outgrowth in sensory neurons.

30 FIG. 3(D) is a representative photomicrograph of a related compound, 2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate, (100 nM) promoting neurite outgrowth in sensory neurons.

FIG. 4 presents quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving compound 1 and related compounds.

DETAILED DESCRIPTION OF THE INVENTIONDefinitions

5 "Alkenyl" means a branched or unbranched unsaturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C₂-C₆ straight or
10 branched alkenyl hydrocarbon chain contains 2 to 6 carbon atoms having at least one double bond, and includes but is not limited to substituents such as ethenyl, propenyl, iso-propenyl, butenyl, iso-butenyl, tert-butenyl, n-pentenyl, n-hexenyl, and the like. It is also contemplated as within the scope of the present invention that "alkenyl" may also refer to an unsaturated hydrocarbon chain wherein any of the carbon atoms of said alkenyl are optionally replaced with O,
15 NH, S, or SO₂. For example, carbon 2 of 4-pentene can be replaced with O to form (2-propene)oxymethyl.

"Alkoxy" refers to the group -OR wherein R is alkyl as herein defined. Preferably, R is a branched or unbranched saturated hydrocarbon chain containing 1 to
20 6 carbon atoms.

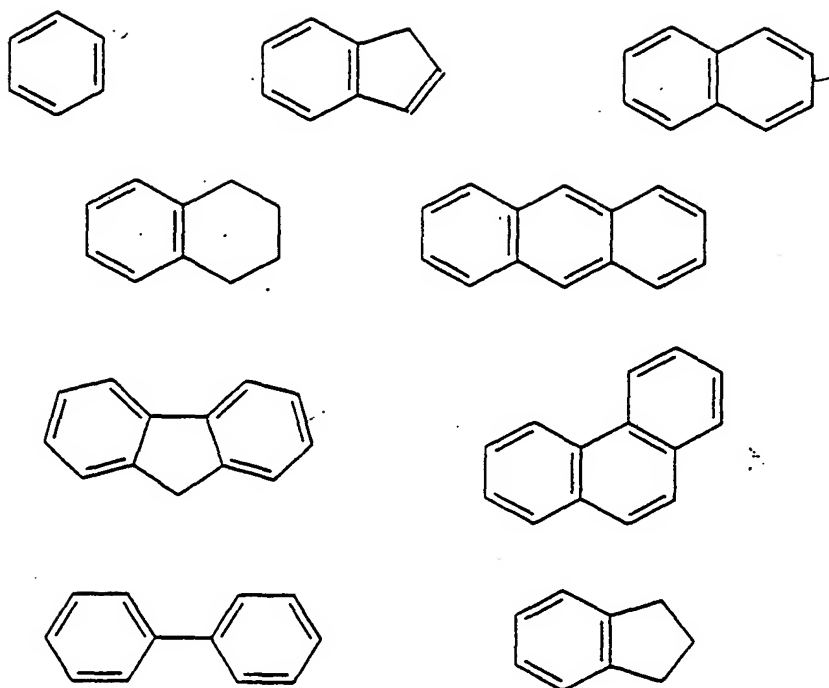
"Alkyl" means a branched or unbranched saturated hydrocarbon chain comprising a designated number of carbon atoms. For example, C₁-C₆ straight or branched alkyl hydrocarbon chain contains 1 to 6 carbon atoms,
25 and includes but is not limited to substituents such as methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, and the like. It is also contemplated as within the scope of the present invention that "alkyl" may also refer to a hydrocarbon chain wherein any of the carbon atoms of said alkyl are optionally replaced with O, NH, S, or SO₂. For example, carbon 2 of n-pentyl can be replaced with O to form propyloxymethyl.
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Throughout this application, "R" or "R_n", where n is
35 a number, is used to designate various substituents.

These R groups are independently selected. Thus, for example, the fact that R_1 may be a branched alkyl in one context does not require that R_1 be the same branched alkyl, and does not prohibit that R_1 be, for example, a straight chain alkenyl in another context in the same molecule. It is intended that all " R_n " are selected independently of all other " R_n ", whether or not the term "independently selected" is used.

"Aryl" or "aromatic" refers to an aromatic carbocyclic or heterocyclic group having a single ring, for example a phenyl ring; multiple rings, for example biphenyl; or multiple condensed rings in which at least one ring is aromatic, for example naphthyl, 1,2,3,4-tetrahydronaphthyl, anthryl, or phenanthryl. The ring(s) of an aryl moiety can be unsubstituted or substituted with one or more substituents including, but not limited to, halo, hydroxyl, nitro, trifluoromethyl, C_1 - C_6 straight or branched chain alkyl or alkenyl, C_1 - C_6 alkoxy, C_1 - C_6 alkenyloxy, phenoxy, benzyloxy, or amino; a heterocyclic ring may contain 1-6 heteroatom(s) selected from the group consisting of O, N, and S. The substituents attached to a phenyl ring portion of an aryl moiety in the compounds of the invention may be configured in the ortho-, meta-, or para-orientation(s), with the para-orientation being preferred.

Examples of typical aryl moieties included in the scope of the present invention may include, but are not limited to, the following:



It should be kept in mind that, throughout this application, "Ar" or "Ar_n", where n is a number, is used to designate various substituents. As indicated throughout, these Ar groups are independently selected. Thus, for example, the fact that Ar may be phenyl in one context does not require that Ar be phenyl, nor prohibit that Ar be, for example, pyridyl in another context in the same molecule. It is intended that all "Ar" are selected independently of all other "Ar", whether or not the term "independently selected" is used.

"Carbocycle" or "carbocyclic" refers to an organic cyclic moiety in which the cyclic skeleton is comprised of only carbon atoms, whereas the term "heterocycle" or "heterocyclic" refers to an organic cyclic moiety in which the cyclic skeleton contains one or more heteroatoms selected from nitrogen, oxygen, or sulfur, and which may or may not include carbon atoms. The term "carbocycle" refers to a carbocyclic moiety containing the indicated number of carbon atoms. The term "C₃-C₈

cycloalkyl", therefore, refers to an organic cyclic substituent in which three to eight carbon atoms form a three, four, five, six, seven, or eight-membered ring, including, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl ring.

"Carbocyclic" or "heterocyclic" each includes within its scope a single ring system, multiple fused rings (for example, bicyclic, tricyclic, or other similar bridged ring systems or substituents, e.g. adamantyl) or multiple condensed ring systems. One skilled in the art, therefore, will appreciate that in the context of the present invention, a cyclic structure may comprise bi-, or tri-, or multiple condensed rings, bridged ring systems, or combinations thereof.

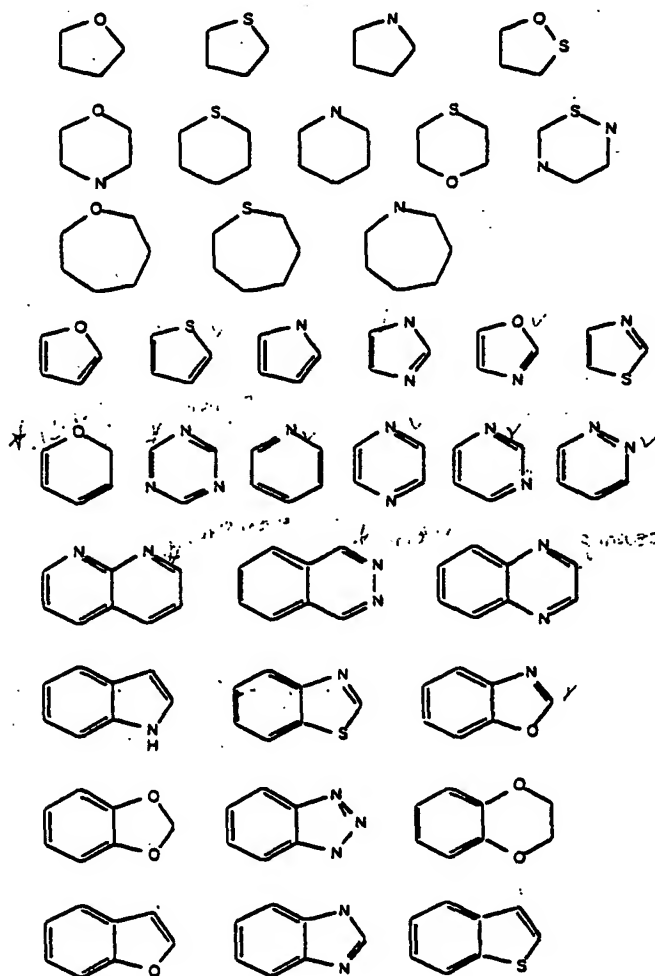
"Halo" refers to fluoro, chloro, bromo or iodo, unless otherwise indicated.

"Heterocycle" or "heterocyclic", refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring, multiple fused rings (for example, bicyclic, tricyclic, or other similar bridged ring systems or substituents), or multiple condensed rings, and having at least one heteroatom such as nitrogen, oxygen, or sulfur within at least one of the rings. This term also includes "Heteroaryl," which refers to a heterocycle in which at least one ring is aromatic. Any heterocyclic or heteroaryl group can be unsubstituted or optionally substituted with one or more groups, as defined above. Further, bi- or tricyclic heteroaryl moieties may comprise at least one ring which is either completely or partially saturated.

As one skilled in the art will appreciate, such heterocyclic moieties may exist in several isomeric forms, all of which are encompassed by the present invention. For example, a 1,3,5-triazine moiety is

isomeric to a 1,2,4-triazine group. Such positional isomers are to be considered within the scope of the present invention. Likewise, the heterocyclic or heteroaryl groups can be bonded to other moieties in the compounds of the present invention. The point(s) of attachment to these other moieties is not to be construed as limiting on the scope of the invention. Thus, by way of example, a pyridyl moiety may be bound to other groups through the 2-, 3-, or 4-position of the pyridyl group. All such configurations are to be construed as within the scope of the present invention.

Examples of heterocyclic or heteroaryl moieties included in the scope of the present invention may include, but are not limited to, the following:



"Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. "Diastereoisomers" are stereoisomers which are not mirror images of each other. "Racemic mixture" means a mixture containing equal parts of individual enantiomers. "Non-racemic mixture" is a mixture containing unequal parts of individual enantiomers or stereoisomers.

"Low molecular weight, small molecule compounds" include, without limitation, molecules which are smaller in size, molecular weight, or both in relation to the compounds Rapamycin, Cyclosporin, and FK506.

"Neurotrophic" includes without limitation the ability to stimulate neuronal regeneration or growth, the ability to prevent or treat neurodegeneration, or both.

"Non-immunosuppressive" refers to the inability of the compounds of the present invention to suppress an immune response when compared to a control such as FK506 or cyclosporin A. Assays for determining immunosuppression are well known to those of ordinary skill in the art. Specific, non-limiting examples of well known assays include PMA and OKT3, wherein mitogens are used to stimulate proliferation of human peripheral blood lymphocytes (PBC) and the tested compounds are evaluated on their ability to inhibit such proliferation.

"Pharmaceutically acceptable carrier" refers to any carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, absorbant, preservative, surfactant, colorant, flavorant, or sweetener. For

these purposes, the compounds of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, intrasternal, and intracranial injection or infusion techniques.

"Pharmaceutically acceptable salt", refers to an organic or inorganic salt which is useful in the treatment of a warm-blooded animal in need thereof. Such salts can be acid or basic addition salts, depending on the nature of the inventive compound to be used.

In the case of an acidic moiety in an inventive compound, a salt may be formed by treatment of the inventive compound with a basic compound, particularly an inorganic base. Preferred inorganic salts are those formed with alkali and alkaline earth metals such as lithium, sodium, potassium, barium, and calcium. Preferred organic base salts include, for example, ammonium, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylamine, dibenzyl-ethylenediamine, and like salts. Other salts of acidic moieties may include, for example, those salts formed with procaine, quinine and N-methylglucosamine, plus salts formed with basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Other suitable base salts, esters, or solvates include magnesium salts; salts with organic bases, such as dicyclohexylamine salts; and N-methyl-D-glucamine. An especially preferred salt is a sodium or potassium salt of an

inventive compound.

With respect to basic moieties, a salt is formed by the treatment of the desired inventive compound with an acidic compound, particularly an inorganic acid.

5 Preferred inorganic salts of this type may include, for example, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric; or like salts. Preferred organic salts of this type, may include, for example, salts formed with formic, acetic, succinic, citric, lactic,

10 maleic, fumaric, palmitic, cholic, pantoic, mucic, d-glutamic, d-camphoric, glutaric, glycolic, phthalic, tartaric, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, para-toluenesulfonic, sorbic, puric, benzoic, cinnamic, and like organic acids. Other

15 suitable acids are adipate, alginate, aspartate, benzenesulfonate, bisulfate, butyrate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, 2-hydroxyethanesulfonate, methanesulfonate, naphthylate, 2-

20 naphthalenesulfonate, nicotinate, oxalate, thiocyanate, tosylate, and undecanoate. An especially preferred salt of this type is a hydrochloride or sulfate salt of the desired inventive compound. Also, the basic nitrogen-

25 containing groups can be quarternized with such agents as: 1) lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; 2) dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates; 3) long chain alkyls such as decyl,

30 lauryl, myristyl, and stearyl substituted with one or more halide such as chloride, bromide, and iodide; and 4) aralkyl halides like benzyl and phenethyl bromide and others.

Also encompassed in the scope of the present

35 invention are pharmaceutically acceptable esters of a

carboxylic acid or hydroxyl containing group, including a metabolically labile ester or a prodrug form of an inventive compound. A metabolically labile ester is one which may produce, for example, an increase in blood levels and prolong the efficacy of the corresponding non-esterified form of the compound. A prodrug form is one which is not in an active form of the molecule as administered but which becomes therapeutically active after some *in vivo* activity or biotransformation, such as, for example, metabolism by enzymatic or hydrolytic cleavage. Esters of an inventive compound may include, for example, methyl, ethyl, propyl, and butyl esters, as well as other suitable esters formed between an acidic moiety and a hydroxyl containing moiety. Metabolically labile esters may include, for example, methoxymethyl, ethoxymethyl, iso-propoxymethyl, α -methoxyethyl, and groups such as α -((C₁-C₄)alkyloxy)ethyl; methoxyethyl, ethoxyethyl, propoxyethyl, and iso-propoxyethyl; 2-oxo-1,3-dioxolen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl; C₁-C₃ alkylthiomethyl groups, for example, methylthiomethyl, ethylthiomethyl, isopropylthiomethyl; acyloxymethyl groups, for example, pivaloyloxy-methyl, α -acetoxymethyl; ethoxycarbonyl-1-methyl; or α -acyloxy- α -substituted methyl groups, for example α -acetoxoethyl.

Further, the compounds of the invention may exist as crystalline solids which can be crystallized from common solvents such as ethanol, N,N-dimethyl-formamide, water, or the like. Thus, crystalline forms of the compounds of the invention may exist as solvates and/or hydrates of the parent compounds or their pharmaceutically acceptable salts, esters, or solvates. All of such forms likewise are to be construed as falling within the scope of the invention.

"Phenyl" refers to any possible isomeric phenyl

radical, optionally monosubstituted or multisubstituted with substituents selected from the group consisting of alkyl, alkoxy, hydroxy, halo, and haloalkyl.

5 "Preventing neurodegeneration" includes (1) the ability to inhibit or prevent neurodegeneration in patients newly diagnosed as having a neurodegenerative disease or at risk of developing a new neurodegenerative disease and (2) the ability to inhibit or prevent further neurodegeneration in patients who are already
10 suffering from, or have symptoms of, a neurodegenerative disease.

"Treating" or "treatment" covers any treatment of a disease, a condition, or both in an animal, particularly a human, and includes:

15 (i) preventing a disease or condition from occurring in a subject which may be predisposed to the disease or condition but has not yet been diagnosed as having it;

(ii) inhibiting a disease or condition, i.e.,
20 arresting its development; or

(iii) relieving a disease or condition, i.e., causing regression of the disease or condition.

"Warm-blooded animal" or "animal" includes a mammal, including a member of the human, equine,
25 porcine, bovine, murine, canine, or feline species. In the case of a human, the term "warm-blooded animal" or "animal" may also be referred to as a "patient". Further, as used herein, "a warm blooded animal in need thereof" refers to a warm-blooded animal which is
30 susceptible to a disorder due to genetic or environmental conditions or predispositions. This term also refers to a warm blooded animal which has already suffered some degree of injury or damage because of genetic or environmental conditions to which the animal
35 has been exposed or to which it is or was predisposed.

Environmental conditions can include treatment with a therapeutic compound, as well as other types of injury or insult.

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Compounds of the Invention

The present invention relates to low molecular weight, small molecule neurotrophic compounds. In a preferred embodiment, the compounds of the present invention do not exert any significant immunosuppressive activity. In another preferred embodiment, the compounds of the present invention may bind to, or otherwise interact with, FKBP-type immunophilins, such as FKBP12; such binding or interaction may inhibit the prolyl-peptidyl cis-trans isomerase, or rotamase, activity of the binding protein.

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In another preferred embodiment, the compound of the present invention has a molecular weight no more than about 800 daltons. In a more preferred embodiment, the compound of the present invention has a molecular weight no more than about 500 daltons. In a particularly preferred embodiment, the compound of the present invention has a molecular weight no more than about 330 daltons.

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In another preferred embodiment, the compound of the present invention exhibits a Chick Dorsal Root Ganglion Neurite Outgrowth Assay ("DRG") ED₅₀ value which is less than about 10 nM. In a more preferred embodiment, the compound of the present invention exhibits a DRG ED₅₀ value which is less than about 1.0 nM. In a particularly preferred embodiment, the compound of the present invention exhibits a DRG ED₅₀ value which is less than about 0.1 nM.

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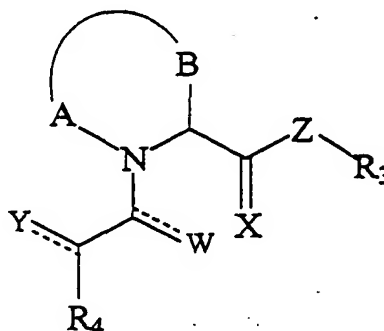
In another preferred embodiment, the compound of the present invention exhibits an MPTP Assay value which is greater than about 20% recovery of TH-stained

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dopaminergic neurons. In a more preferred embodiment, the compound of the present invention exhibits an MPTP Assay value which is greater than about 35% recovery of TH-stained dopaminergic neurons. In a particularly preferred embodiment, the compound of the present invention exhibits an MPTP Assay value which is greater than about 50% recovery of TH-stained dopaminergic neurons.

FORMULA I

A preferred embodiment of this invention is a compound of formula I:



I

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing any combination of CH₂, O, S, SO, SO₂, NH, or NR, in any chemically stable oxidation state;

X is either O or S;

Z is either S, CH₂, CHR₁, CR₁R₂, or a bond;

W and Y are independently O, S, CH₂, or H₂;

R₁, R₂, and R₃ are independently C₁-C₆ straight or branched chain alkyl or alkenyl, which is substituted in one or more position(s) with (Ar₁)_n, (Ar₁)_n connected by a C₁-C₆ straight or branched chain alkyl or alkenyl, C₃-C₉ cycloalkyl, C₃-C₉ cycloalkyl connected by a C₁-C₆ straight

or branched chain alkyl or alkenyl, or Ar₂;

n is 1 or 2;

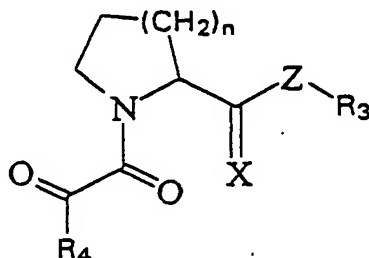
R₄ is either C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₃-C₆ cycloalkyl, C₅-C₆ cycloalkenyl or Ar₁, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted in one or more position(s) with C₁-C₄ straight or branched chain alkyl or alkenyl, or hydroxyl; and

Ar₁ and Ar₂ are each, independently, an aryl group. A preferred embodiment of an aryl group is a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one or more position(s) with halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl or alkenyl, C₁-C₄ alkoxy, C₁-C₄ alkenyloxy, phenoxy, benzyloxy, or amino; wherein the individual ring sizes are 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) selected from the group consisting of O, N, and S.

Suitable mono- and bicyclic, carbo- and heterocyclic rings include, without limitation, naphthyl, indolyl, thioindolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl, phenyl, and benzyl.

FORMULA II

Another preferred embodiment of this invention is a compound of formula II:



II

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

n is 1 or 2;

X is O or S;

5 Z is selected from the group consisting of S, CH₂, CHR₁, CR₁R₂ and a bond;

 R₁, R₂, and R₃ are independently selected from the group consisting of C₁-C₅ straight or branched chain alkyl, C₂-C₅ straight or branched chain alkenyl, and Ar, wherein said R₁, R₂, or R₃ is unsubstituted or substituted with one or more halo, trifluoromethyl, nitro, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, hydroxy, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, amino, or Ar;

15 R₄ is selected from the group consisting of C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, and Ar; and

 Ar is aryl. A preferred embodiment for Ar is phenyl, benzyl, pyridyl, fluorenyl, thioindolyl, or naphthyl, wherein said Ar is unsubstituted or substituted with one or more substituents independently selected from the group consisting of halo, trifluoromethyl, hydroxy, nitro, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino.

 A particularly preferred embodiment of Formula II is a compound wherein n is 1, X is O, Z is CH₂, R₃ is 3-pyridylpropyl, and R₄ is 1,1-dimethylpropyl.

 Another particularly preferred embodiment of Formula II is a compound wherein n is 2, X is O, Z is CH₂, R₃ is 4-phenylbutyl, and R₄ is 1,1-dimethylpropyl.

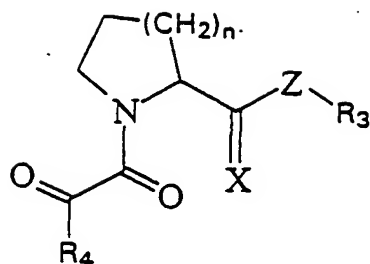
 Another particularly preferred embodiment of Formula II is a compound wherein n is 1, X is O, Z is

CH₂, R₃ is 2-phenylethyl, and R₄ is tert-butyl.

Another particularly preferred embodiment of Formula II is a compound wherein n is 1, X is O, Z is CH₂, R₃ is 3-(4-hydroxyphenyl)propyl, and R₄ is 1,1-dimethylpropyl.

The most preferred embodiments of Formula II are (2S)-3,3-dimethyl-1-[2-(5-(3-pyridyl)pyrrolidinyl)pentane-1,2-dione; 2-((1-oxo-6-phenyl)hexyl) (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)piperidine; 2-(1-Oxo-4-phenyl)-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine; and (2S)-3,3-dimethyl-1-[2-(5-(4-hydroxyphenyl)pentanoyl)pyrrolidinyl]pentane-1,2-dione.

Specific examples of the embodiments of Formula II are presented in TABLE I. The molecular weights of the specifically exemplified compounds is between about 330 daltons and about 500 daltons.



5

TABLE I

	No.	n	X	Z	R ₃	R ₄
10	1	1	O	CH ₂	3-Phenylpropyl	1,1-Dimethylpropyl
	2	1	O	CH ₂	3-(3-Pyridyl)propyl	1,1-Dimethylpropyl
	3	1	O	CH ₂	3-Phenylpropyl	tert-Butyl
	4	1	O	CH ₂	3-(3-Pyridyl)propyl	tert-Butyl
	5	1	O	CH ₂	3-(3-Pyridyl)propyl	Cyclohexyl
15	6	1	O	CH ₂	3-(3-Pyridyl)propyl	Cyclopentyl
	7	1	O	CH ₂	3-(3-Pyridyl)propyl	Cycloheptyl
	8	1	O	CH ₂	2-(9-Fluorenyl)ethyl	1,1-Dimethylpropyl
	9	1	O	S	2-Phenethyl	1,1-Dimethylpropyl
	10	2	O	S	2-Phenethyl	1,1-Dimethylpropyl
20	11	1	O	S	Methyl(2-thioindole)	1,1-Dimethylpropyl
	12	1	O	S	2-Phenethyl	Cyclohexyl
	13	2	O	S	2-Phenethyl	tert-Butyl
	14	2	O	S	2-Phenethyl	Phenyl
	15	1	O	CH ₂	3-(4-Methoxyphenyl)propyl	1,1-Dimethylpropyl
25	16	2	O	CH ₂	4-(4-Methoxyphenyl)butyl	1,1-Dimethylpropyl
	17	2	O	CH ₂	4-Phenylbutyl	1,1-Dimethylpropyl
	18	2	O	CH ₂	4-Phenylbutyl	Phenyl
	19	2	O	CH ₂	4-Phenylbutyl	tert-Butyl
	20	1	S	CH ₂	3-Phenylpropyl	1,1-Dimethylpropyl
30	21	1	S	S	2-Phenethyl	1,1-Dimethylpropyl
	22	2	S	CH ₂	3-Phenylpropyl	1,1-Dimethylpropyl
	23	2	S	S	2-Phenethyl	1,1-Dimethylpropyl
	24	1	O	S	2-Phenethyl	Cyclopentyl

TABLE I (continued)

	No.	n	X	Z	R ₃	R ₄
5	25	2	O	S	3-Phenylpropyl	tert-Butyl
	26	1	O	S	3-Phenylpropyl	1,1-Dimethylpropyl
	27	1	O	S	3-(3-Pyridyl)propyl	1,1-Dimethylpropyl
	28	1	O	S	3-Phenylpropyl	Cyclohexyl
	29	1	O	S	4-Phenylbutyl	Cyclohexyl
10	30	1	O	S	4-Phenylbutyl	1,1-Dimethylpropyl
	31	1	O	S	3-(3-Pyridyl)propyl	Cyclohexyl
	32	1	O	S	3,3-Diphenylpropyl	1,1-Dimethylpropyl
	33	1	O	S	3,3-Diphenylpropyl	Cyclohexyl
	34	1	O	S	3-(4-Methoxyphenyl)propyl	1,1-Dimethylpropyl
15	35	2	O	S	4-Phenylbutyl	tert-Butyl
	36	2	O	S	1,5-Diphenyl-3-pentyl	1,1-Dimethylpropyl
	37	2	O	S	1,5-Diphenyl-3-pentyl	Phenyl
	38	2	O	S	3-(4-Methoxyphenyl)propyl	1,1-Dimethylpropyl
20	39	2	O	S	3-(4-Methoxyphenyl)propyl	Phenyl
	40	2	O	S	3-(1-Naphthyl)propyl	1,1-Dimethylpropyl
	41	1	O	S	3,3-Di(4-fluoro)phenyl-propyl	1,1-Dimethylpropyl
25	42	1	O	S	4,4-Di(4-fluoro)phenyl-butyl	1,1-Dimethylpropyl
	43	1	O	S	3-(1-Naphthyl)propyl	1,1-Dimethylpropyl
	44	1	O	S	2,2-Diphenylethyl	1,1-Dimethylpropyl
	45	2	O	S	2,2-Diphenylethyl	1,1-Dimethylpropyl
30	46	2	O	S	3,3-Diphenylpropyl	1,1-Dimethylpropyl
	47	1	O	S	3-(4-{Trifluoromethyl}-phenyl)propyl	1,1-Dimethylpropyl
	48	1	O	S	3-(2-Naphthyl)propyl	1,1-Dimethylpropyl

TABLE I (continued)

	No.	n	X	Z	R ₃	R ₄
5	49	2	O	S	3-(1-Naphthyl)propyl	1,1-Dimethylpropyl
	50	1	O	S	3-(3-Chloro)phenylpropyl	1,1-Dimethylpropyl
	51	1	O	S	3-(3-{Trifluoromethyl}-phenyl)propyl	1,1-Dimethylpropyl
10	52	1	O	S	3-(2-Biphenyl)propyl	1,1-Dimethylpropyl
	53	1	O	S	3-(2-Fluorophenyl)propyl	1,1-Dimethylpropyl
	54	1	O	S	3-(3-Fluorophenyl)propyl	1,1-Dimethylpropyl
	55	2	O	S	4-Phenylbutyl	1,1-Dimethylpropyl
	56	2	O	S	3-Phenylpropyl	1,1-Dimethylpropyl
15	57	1	O	S	3-(2-Chloro)phenylpropyl	1,1-Dimethylpropyl
	58	2	O	S	3-(3-Chloro)phenylpropyl	1,1-Dimethylpropyl
	59	2	O	S	3-(2-Fluoro)phenylpropyl	1,1-Dimethylpropyl
	60	2	O	S	3-(3-Fluoro)phenylpropyl	1,1-Dimethylpropyl
	61	1	O	S	3-(3,4-Dimethoxyphenyl)-propyl	1,1-Dimethylpropyl
20	62	1	O	CH ₂	3-Phenylpropyl	Cyclohexyl
	63	1	O	CH ₂	2-Phenylethyl	tert-Butyl
	64	2	O	CH ₂	4-Phenylbutyl	Cyclohexyl
	65	2	O	CHR ₁	2-Phenylethyl	tert-Butyl
	66	1	O	CH ₂	3,3-Di(4-fluorophenyl)-propyl	1,1-Dimethylpropyl
25	67	2	O	CH ₂	3-Phenylpropyl	1,1-Dimethylpropyl
	68	1	O	CH ₂	3-(4-Hydroxyphenyl)propyl	1,1-Dimethylpropyl
	69	1	O	bond	3-Phenylpropyl	1,1-Dimethylpropyl
	70	1	O	bond	3-(3-Pyridyl)propyl	tert-Butyl
	71	1	O	bond	3-(3-Pyridyl)propyl	Cyclohexyl
30	72	2	O	bond	4-(4-Methoxyphenyl)butyl	1,1-Dimethylpropyl
	73	2	O	bond	4-Phenylbutyl	1,1-Dimethylpropyl
	74	2	O	bond	4-Phenylbutyl	Phenyl

The most preferred examples of the compounds of TABLE I are named as follows:

- | | | |
|----|----|---|
| | 1 | (2S)-3,3-dimethyl-1-[2-(5-phenylpentanoyl)pyrrolidinyl]pentane-1,2-dione |
| 5 | 2 | (2S)-3,3-dimethyl-1-[2-(5-(3-pyridyl)pyrrolidinyl]pentane-1,2-dione |
| | 3 | (2S)-2-((1-oxo-5-phenyl)-pentyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine |
| | 9 | 2-Phenyl-1-ethyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate |
| 10 | 10 | 2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate |
| | 11 | 1-(2-benzo[b]thiophen-3-ylmethylthio)carbonyl]pyrrolidinyl)-3,3-dimethylpentane-1,2-dione |
| 15 | 12 | 2-Phenyl-1-ethyl (2S)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate |
| | 14 | 2-Phenyl-1-ethyl 1-(2-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate |
| | 17 | 2-((1-oxo-6-phenyl)-hexyl) (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)piperidine |
| 20 | 24 | 2-Phenyl-1-ethyl (2S)-1-(1-cyclopentyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate |
| | 25 | 3-Phenyl-1-propyl 1-(3,3-dimethyl-1,2-dioxobutyl)-2-piperidinecarbothioate |
| 25 | 26 | 3-Phenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate |
| | 27 | 3-(3-Pyridyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate |
| | 28 | 3-Phenyl-1-propyl (2S)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate |
| 30 | 29 | 4-Phenyl-1-butyl (2S)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate |
| | 30 | 4-Phenyl-1-butyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate |

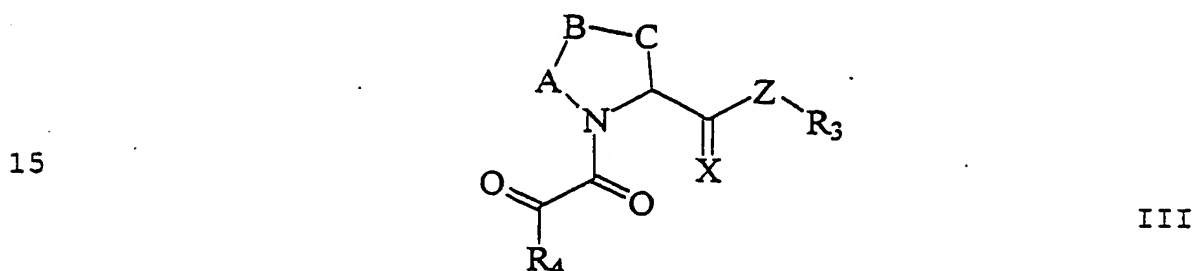
- 31 3-(3-Pyridyl)-1-propyl (2S)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate
- 32 3,3-Diphenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate
- 5 33 3,3-Diphenyl-1-propyl (2S)-1-(2-cyclohexyl-1,2-dioxoethyl)-2-pyrrolidinecarbothioate
- 34 3-(para-Methoxyphenyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate
- 35 4-Phenyl-1-butyl 1-(1,2-dioxo-3,3-dimethylbutyl)-2-piperidinecarbothioate
- 10 36 1,5-Diphenyl-3-pentyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate
- 37 1,5-Diphenyl-3-pentyl 1-(2-phenyl-1,2-dioxoethyl)-2-piperidinecarbothioate
- 15 38 3-(para-Methoxyphenyl)-1-propyl 1-(1,2-dioxo-3,3-dimethylpentyl)piperidine-2-carbothioate
- 39 3-(para-Methoxyphenyl)-1-propyl 1-(2-phenyl-1,2-dioxoethyl)piperidine-2-carbothioate
- 40 3-(1-Naphthyl)-1-propyl 1-(3,3-dimethyl-1,2-dioxopentyl)piperidine-2-carbothioate
- 20 41 3,3-Di(para-fluoro)phenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate
- 42 4,4-Di(para-fluorophenyl)butyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 25 43 3-(1-Naphthyl)-1-propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 44 2,2-Diphenylethyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 45 2,2-Diphenylethyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate
- 30 46 3,3-Diphenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate
- 47 3-[4-(Trifluoromethyl)phenyl]propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate

- 48 3-(2-Naphthyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 49 3-(1-Naphthyl)-1-propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate
- 5 50 3-(3-Chlorophenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 51 3-[3-(Trifluoromethyl)phenyl]propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 52 3-(2-Biphenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 10 53 3-(2-Fluorophenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 54 3-(3-Fluorophenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 15 55 4-Phenylbutyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate
- 56 3-Phenylpropyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate
- 57 3-(2-Chlorophenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 20 58 3-(3-Chlorophenyl)-1-propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate
- 59 3-(2-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate
- 25 60 3-(3-Fluorophenyl)propyl 1-(3,3-dimethyl-2-oxopentanoyl)-2-piperidinecarbothioate
- 61 3-(3,4-Dimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)-2-pyrrolidinecarbothioate
- 62 (2S)-2-((1-Oxo-5-phenyl)pentyl-1-(2-Cyclohexyl-1,2-dioxoethyl)pyrrolidine
- 30 63 2-(1-Oxo-4-phenyl)-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine
- 64 2-(1-Oxo-6-phenyl)-hexyl-1-(2-Cyclohexyl-1,2-dioxoethyl)piperidine
- 35 65 2-((1-Oxo-[2-(2'-phenyl)ethyl]-4-phenyl)-butyl-1-

- (3,3-dimethyl-1,2-dioxobutyl)piperidine
- 66 (2S)-2-[5,5-di(4-Fluorophenyl)pentanoyl]-1-(3,3-dimethyl-1,2-pentanedione)pyrrolidine
- 67 3,3-Dimethyl-1-[2-(5-phenylpentanoyl)piperidino]-1,2-pentanedione
- 5 68 (2S)-3,3-dimethyl-1-[2-(5-(4-hydroxyphenyl)pentanoyl)pyrrolidinyl]pentane-1,2-dione

FORMULA III

10 Another preferred embodiment is a compound of formula III:



or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

- 20 A, B, and C are independently CH₂, O, S, SO, SO₂, NH, or NR₄;

X is O or S;

Z is S, CH₂, CHR₁, or CR₁R₂;

- 25 R₁, R₂, and R₃ are independently C₁-C₆ straight or branched chain alkyl or alkenyl, which is substituted in one or more position(s) with (Ar₁)_n, (Ar₁)_n connected by a C₁-C₆ straight or branched chain alkyl or alkenyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl connected by a C₁-C₆ straight or branched chain alkyl or alkenyl, Ar₂, or a combination thereof;
- 30

n is 1 or 2;

- 35 R₄ is either C₁-C₆ straight or branched chain alkyl or alkenyl, C₃-C₈ cycloalkyl, C₃-C₇ cycloalkenyl or Ar₁, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted in one or more

position(s) with C₁-C₆ straight or branched chain alkyl or alkenyl, hydroxyl, or a combination thereof; and

Ar₁ and Ar₂ are independently a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted in one to three position(s) with halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl or alkenyl, C₁-C₆ alkoxy, C₁-C₆ alkenyloxy, phenoxy, benzyloxy, amino or a combination thereof; wherein the individual ring sizes are 5-6 members; and wherein the heterocyclic ring contains 1-6 heteroatom(s) selected from the group consisting of O, N, S, and a combination thereof.

Particularly preferred compounds of formula III are presented in TABLE II.

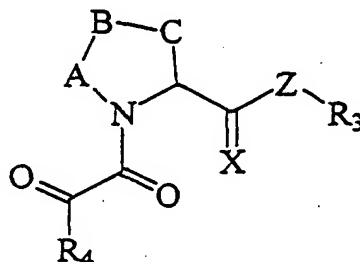
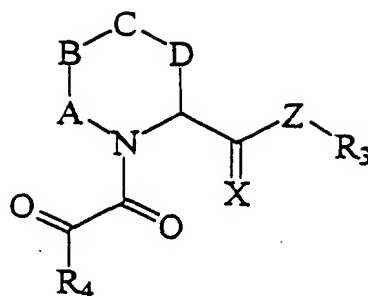


TABLE II

No.	A	B	C	X	Z	R ₃	R ₄
75	CH ₂	S	CH ₂	O	S	2-phenethyl	1,1-Dimethylpropyl
76	CH ₂	S	CH ₂	O	CH ₂	3-phenylpropyl	1,1-Dimethylpropyl
77	CH ₂	CH ₂	NH	O	S	2-phenethyl	1,1-Dimethylpropyl
78	CH ₂	S	CH ₂	S	S	2-phenethyl	1,1-Dimethylpropyl

FORMULA IV

A further preferred embodiment of this invention is a compound of formula IV:



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

10 A, B, C, and D are independently CH₂, O, S, SO, SO₂, NH, or NR₄;

 X is O or S;

 Z is S, CH₂, CHR₁, or CR₁R₂;

 R₁, R₂, and R₃ are independently C₁-C₆ straight or
 15 branched chain alkyl or alkenyl, which is substituted in one or more position(s) with (Ar₁)_n, (Ar₁)_n connected by a C₁-C₆ straight or branched chain alkyl or alkenyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl connected by a C₁-C₆ straight or branched chain alkyl or alkenyl, Ar₂, or a combination thereof;
 20

 n is 1 or 2;

 R₄ is either C₁-C₆ straight or branched chain alkyl or alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl or Ar₁, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl
 25 is either unsubstituted or substituted in one or more position(s) with C₁-C₄ straight or branched chain alkyl or alkenyl, hydroxyl, or a combination thereof; and

 Ar₁ and Ar₂ are independently a mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring
 30 is either unsubstituted or substituted in one to three position(s) with halo, hydroxyl, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl or alkenyl, C₁-C₄ alkoxy, C₁-C₄ alkenyloxy, phenoxy, benzyloxy, amino, or a combination thereof; wherein the individual ring sizes
 35 are 5-6 members; and wherein the heterocyclic ring

contains 1-6 heteroatom(s) selected from the group consisting of O, N, S, and a combination thereof.

Particularly preferred compounds of formula IV are presented in TABLE III.

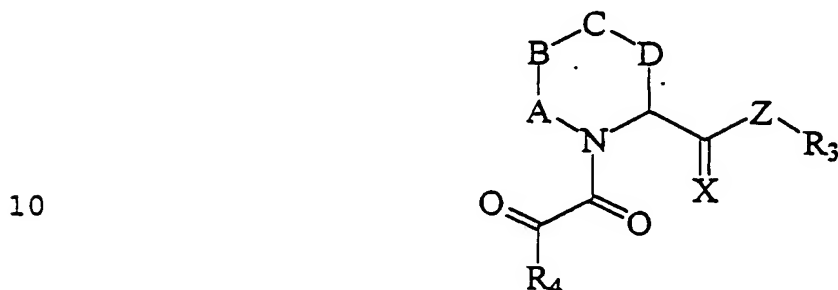


TABLE III

15

No.	A	B	C	D	X	Z	R ₃	R ₄
79	CH ₂	CH ₂	O	CH ₂	O	CH ₂	3-phenylpropyl	1,1-Dimethylpropyl
80	CH ₂	CH ₂	O	CH ₂	O	S	2-phenethyl	1,1-Dimethylpropyl
81	CH ₂	CH ₂	S	CH ₂	O	CH ₂	3-phenylpropyl	1,1-Dimethylpropyl
82	CH ₂	CH ₂	S	CH ₂	O	S	2-phenethyl	1,1-Dimethylpropyl

20

The compounds of this invention possess at least one asymmetric center and thus can be produced as mixtures of stereoisomers or as individual R- and S-stereoisomers. The individual enantiomers may be obtained by using an optically active starting material, by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis, or by resolving a compound of the present invention. It is understood that the individual R- and S-stereoisomers as well as mixtures (racemic and non-racemic) of stereoisomers are encompassed by this invention. The S-stereoisomer is most preferred.

25

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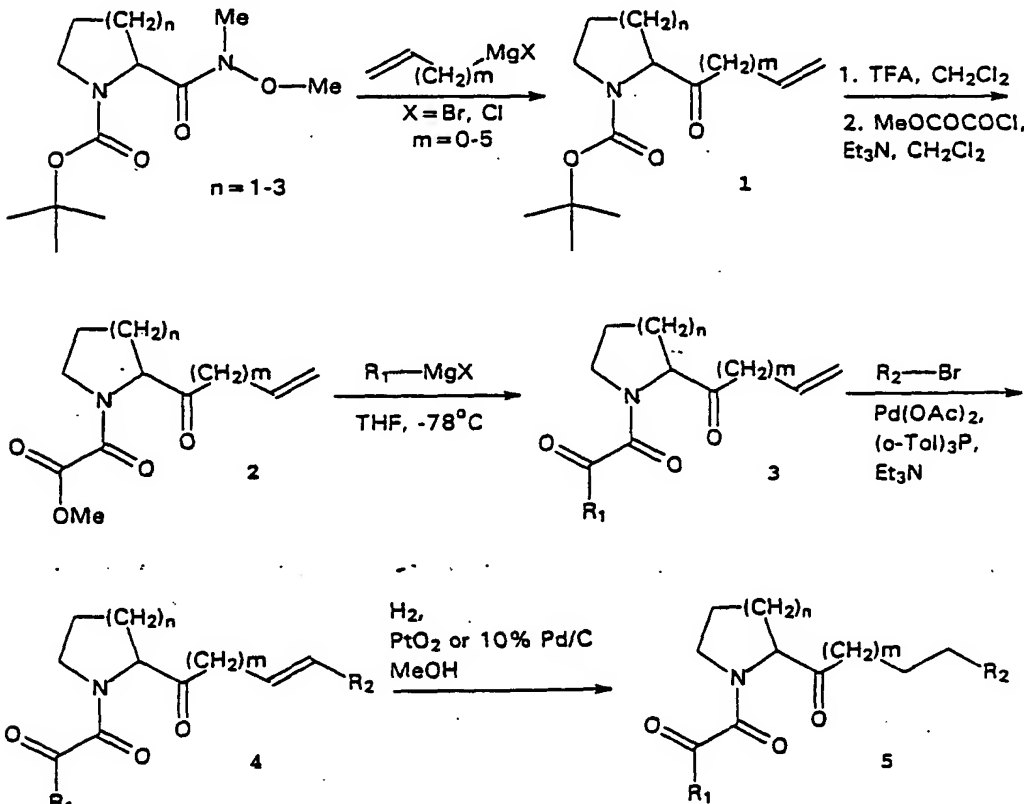
Synthesis of Pyrrolidine Derivatives

35

The compounds of formulas I to IV may be prepared

15

SCHEME I



Methods of Using the Compounds of the Invention

5 The present invention further relates to the use of a compound of the present invention in the preparation of a medicament for effecting a neuronal activity in an animal.

Further, the present invention relates to a method of effecting a neuronal activity in an animal, comprising administering to said animal a neurotrophically effective amount of a compound of the
10 present invention.

As neurotrophic agents, the compounds of this invention can be periodically administered to a patient undergoing treatment for neurological disorders or for other reasons in which it is desirable to stimulate
15 neuronal regeneration and growth, such as in various peripheral neuropathic and neurological disorders relating to neurodegeneration. The compounds of this invention can also be administered to mammals other than humans for treatment of various mammalian neurological
20 disorders.

The novel compounds of the present invention possess an excellent degree of neurotrophic activity. This activity is useful in the stimulation of damaged neurons, the promotion of neuronal regeneration, the
25 prevention of neurodegeneration, and in the treatment of several neurological disorders known to be associated with neuronal degeneration and peripheral neuropathies. The neurological disorders that may be treated include but are not limited to: trigeminal neuralgia,
30 glossopharyngeal neuralgia, Bell's Palsy, myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed invertebrate disk syndromes, cervical
35 spondylosis, plexus disorders, thoracic outlet

destruction syndromes, peripheral neuropathies such as those caused by lead, dapsone, ticks, porphyria, Gullain-Barré syndrome, Alzheimer's disease, Huntington's Disease, or Parkinson's disease.

5 For these purposes, the compounds may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, or via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-
10 acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneally, intrathecally, intraventricularly, intrasternal, and intracranial injection or infusion techniques.

15 To be effective therapeutically as central nervous system targets, the compounds should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier can be effectively administered by an intraventricular
20 route.

 The compounds may be administered in the form of sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions. These suspensions, may be formulated according to techniques
25 known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparations may also be sterile injectable solutions or suspensions in non-toxic parenterally-acceptable diluents or solvents, for example, as solutions in 1,3-
30 butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as solvents or suspending mediums. For this purpose, any
35 bland fixed oil such as a synthetic mono- or di-

glyceride may be employed. Fatty acids such as oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are useful in the preparation of injectables.

5 These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

Additionally, the compounds may be administered orally in the form of capsules, tablets, aqueous suspensions, or solutions. Tablets may contain carriers
10 such as lactose and corn starch, and/or lubricating agents such as magnesium stearate. Capsules may contain diluents including lactose and dried corn starch. Aqueous suspensions may contain emulsifying and suspending agents combined with the active ingredient.
15 The oral dosage forms may further contain sweetening, flavoring, coloring agents, or combinations thereof.

The compounds may also be administered rectally in the form of suppositories. These compositions can be prepared by mixing the drug with a suitable non-
20 irritating excipient which is solid at room temperature, but liquid at rectal temperature and, therefore, will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax, and polyethylene glycols.

Furthermore, the compounds may be administered
25 topically, especially when the conditions addressed for treatment involve areas or organs readily accessible by topical application, including neurological disorders of the eye, the skin, or the lower intestinal tract. Suitable topical formulations can be readily prepared
30 for each of these areas.

For topical application to the eye, or ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as a solution in isotonic, pH adjusted
35 sterile saline, either with or without a preservative

such as benzylalkonium chloride. Alternatively, the compounds may be formulated into ointments, such as petrolatum, for ophthalmic use.

5 For topical application to the skin, the compounds can be formulated into suitable ointments containing the compounds suspended or dissolved in, for example, mixtures with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, 10 emulsifying wax, and water. Alternatively, the compounds can be formulated into suitable lotions or creams containing the active compound suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, 15 polysorbate 60, cetyl ester wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water.

Topical application to the lower intestinal tract can be effected in a rectal suppository formulations (see above) or in suitable enema formulations.

20 Dosage levels on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 0.1 mg to about 1,000 mg. The amount of active ingredient that may be combined with the carrier 25 materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a 30 variety of factors, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; drug combination; the severity of the particular disease being treated; 35 and the form of administration.

As neurotrophic agents, the compounds can be administered with other neurotrophic agents such as neurotrophic growth factor, brain derived growth factor, glial derived growth factor, ciliary neurotrophic factor, insulin growth factor and active truncated derivatives thereof, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factors, neurotrophin-3, and neurotrophin 4/5. The dosage level of other neurotrophic drugs will depend upon the factors previously stated and the neurotrophic effectiveness of the drug combination.

The neurotrophic compounds of this invention can be periodically administered to a patient undergoing treatment for neurological disorders or for other reasons in which it is desirable to stimulate neuronal regeneration and growth, such as in various peripheral neuropathic and neurological disorders relating to neurodegeneration. The compounds of this invention can also be administered to mammals other than humans for treatment of various mammalian neurological disorders.

Pharmaceutical Compositions of the Invention

The present invention also relates to a pharmaceutical composition comprising:

- (i) an effective amount of a compound of the present invention; and
- (ii) a pharmaceutically acceptable carrier.

In a preferred embodiment, such pharmaceutical composition is effective for effecting a neuronal activity, for treating neurodegenerative diseases, neurological disorders, and nerve damage, or for promoting nerve growth in an animal.

The above discussion relating to the utility and administration of the compounds of the present invention

also applies to the pharmaceutical compositions of the present invention.

EXAMPLES

5 The following examples are illustrative of the present invention and are not intended to be limitations thereon. Unless otherwise specified, all percentages are based on 100% by weight of the final compound.

10

EXAMPLE 1

Synthesis of (2S)-2-((1-oxo-5-phenyl)-pentyl-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine (1)

(2S)-2-(1-oxo-5-phenyl)pentyl-N-benzylpyrrolidine.
 1-chloro-4-phenylbutane (1.78 g; 10.5 mmol) in 20 mL of
 15 THF was added to 0.24 g (10 mmol) of magnesium turnings in 50 mL of refluxing THF. After the addition was complete, the mixture was refluxed for an additional 5 hours, and then added slowly to a refluxing solution of N-benzyl-L-proline ethyl ester (2.30 g (10 mmol) in 100
 20 mL of THF. After 2 hours of further reflux, the mixture was cooled and treated with 5 mL of 2 N HCl. The reaction mixture was diluted with ether (100 mL) and washed with saturated NaHCO₃, water and brine. The organic phase was dried, concentrated and
 25 chromatographed, eluting with 5:1 CH₂Cl₂:EtOAc to obtain 2.05 g (64%) of the ketone as an oil, ¹H NMR (CDCl₃; 300 MHz): 1.49-2.18 (m, 8H); 2.32-2.46 (m, 1H); 2.56-2.65 (m, 2H); 2.97-3.06 (m, 1H); 3.17-3.34 (m, 1H); 3.44-3.62 (m, 1H); 4.02-4.23 (m, 2H); 7.01-7.44 (m, 10H).

30 (2S)-2-(1-oxo-5-phenyl)pentylpyrrolidine. The ketone compound (500 mg) and palladium hydroxide (20% on carbon, 50 mg) was hydrogenated at 40 psi in a Paar shaker overnight. The catalyst was removed by filtration and the solvent was removed in vacuo. The

free amine was obtained as a yellow oil (230 mg; 100%), ^1H NMR (CDCl_3 ; 300 MHz): 1.75-2.34 (m, 10H); 2.55 (m, 2H); 2.95 (dm, 1H); 3.45-3.95 (m, 1H); 4.05 (m, 1H); 7.37 (m, 5H).

5 (2S)-2-(1-oxo-5-phenyl)pentyl-1-(1,2-dioxo-2-methoxyethyl)pyrrolidine. To a solution of (2S)-2-(1-oxo-4-phenyl)butylpyrrolidine (230 mg; 1.0 mmol) in CH_2Cl_2 (20 mL) at 0°C was added dropwise methyloxalyl chloride (135 mg; 1.1 mmol). After stirring at 0°C for
10 3 hours, the reaction was quenched with saturated NH_4Cl and the organic phase was washed with water and brine and dried and concentrated. The crude residue was purified on a silica gel column, eluting with 20:1 CH_2Cl_2 :EtOAc to obtain 300 mg of the oxamate as a clear
15 oil (98%), ^1H NMR (CDCl_3 ; 300 MHz): 1.68 (m, 4H); 1.91-2.38 (m, 4H); 2.64 (t, 2H); 3.66-3.80 (m, 2H); 3.77, 3.85 (s, 3H total); 4.16 (m, 2H); 4.90 (m, 1H); 7.16 (m, 3H); 7.27 (m, 2H).

20 (2S)-2-((1-oxo-5-phenyl)-pentyl-1-(3,3-dimethyl-1,2-dioxopentyl)pyrrolidine (1). To a solution of the oxamate above (250 mg; 0.79 mmol) in anhydrous ether (15 mL), cooled to -78°C , was added 1,1-dimethylpropylmagnesium chloride (0.8 mL of a 1.0 M solution in ether; 0.8 mmol). After stirring the resulting mixture at
25 -78°C for 2 hours, the reaction was quenched by the addition of 2 mL of saturated NH_4Cl , followed by 100 mL of EtOAc. The organic phase was washed with brine, dried, concentrated, and purified on a silica gel column, eluting with 50:1 CH_2Cl_2 :EtOAc. Compound 1 was
30 obtained as a clear oil, 120 mg, ^1H NMR (CDCl_3 , 300 MHz): δ 0.87 (t, 3H, $J=7.5$); 1.22 (s, 3H); 1.25 (s, 3H); 1.67 (m, 4H); 1.70-2.33 (m, 6H); 2.61 (t, 2H, $J=7.1$); 3.52 (m, 2H); 4.17 (t, 2H, $J=6.2$); 4.52 (m, 1H); 7.16-7.49 (m, 5H). Anal. Calcd. for $\text{C}_{22}\text{H}_{31}\text{NO}_3 - \text{H}_2\text{O}$: C, 70.37; H, 8.86;
35 N, 3.73. Found: 70.48; H, 8.35; N, 3.69.

EXAMPLE 2Synthesis of 2-((1-oxo-6-phenyl)hexyl) (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)piperidine (17)

The method of Example 1 was utilized to prepare 2-
 5 ((1-oxo-6-phenyl)hexyl) (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)piperidine (17), utilizing 2-(ethoxy carboxylate)N-benzylpiperidine and 1-chloro-5-phenyl pentane as the starting materials.

EXAMPLE 3

10 Synthesis of 2-(1-Oxo-4-phenyl)butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine (63)

The method of Example 1 was utilized to prepare 2-
 (1-Oxo-4-phenyl)butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine (63), utilizing 1-chloro-4-(4-
 15 hydroxyphenyl)butane, for 1-chloro-4-phenylbutane, as a starting material.

EXAMPLE 4

Synthesis of (2S)-3,3-dimethyl-1-[2-(5-(3-pyridyl)pyrrolidinyl)pentane-1,2-dione (2)

20 Tert-butyl 2-pent-4-enoylpyrrolidinecarboxylate.
 To a solution of 3-butenylmagnesiumbromide (97 ml of a 0.5 M solution; 48.4 mmol) in THF (15 ml), cooled to 0° C and under a nitrogen atmosphere, was added dropwise with stirring a solution of tert-butyl 2-(N-methoxy-N-
 25 methylcarbamoyl)pyrrolidine carboxylate (5.0 g, 19.4 mmol) in 15 ml of THF. The mixture was stirred overnight while slowly coming to room temperature. The reaction was quenched by the addition of 80 ml saturated NH₄Cl followed by 50 ml of ethyl acetate and 20 ml of
 30 water. The layers were separated, and the aqueous layer was extracted with 2 X 100 ml ethyl acetate. The combined organic layers were dried over MgSO₄, filtered, concentrated, and the crude product was purified on a silica gel column with 10% ethyl acetate in hexane to

obtain the olefin tert-butyl 2-pent-4-enoylpyrrolidine carboxylate as a clear oil, 4.30 g (88%): ^1H NMR (CDCl_3 , 400 MHz): d.

Methyl 2-oxo-2-(2-pent-4-enoylpyrrolidinyl)acetate.

5 Trifluoroacetic acid ("TFA"; 65.7 g; 576 mmol) was added dropwise to a solution of 24.3 g (96 mmol) of tert-butyl (2-pent-4-enoyl)pyrrolidinecarboxylate in 45 ml of CH_2Cl_2 , cooled to 0°C . After stirring for 4 hours, Thin Layer Chromatography ("TLC") indicated that the reaction
10 was complete, and the mixture was concentrated in vacuo to remove TFA. The residue was dissolved in 800 ml of CH_2Cl_2 and treated with 2 equivalents of triethylamine while stirring and cooling the mixture in an ice bath. Methyl oxalyl chloride (13.5 g; 106 mmol) was added as
15 a solution in 40 ml CH_2Cl_2 , in 10 ml portions each followed by 5 ml of Et_3N . After the addition, a final 10 ml portion of Et_3N was added and the mixture was stirred overnight. It was concentrated, treated with 100 ml of 1:1 ethyl acetate/hexane), filtered to remove solids,
20 and the concentrated residue purified by SGC, eluting with 1:1 hexane/ethyl acetate, to obtain the oxamate methyl 2-oxo-2-(2-pent-4-enoylpyrrolidinyl)acetate as a brownish oil, 18.80 g (82%). ^1H NMR (CDCl_3 , 400 MHz): d.

3,3-Dimethyl-1-(2-pent-4-enoylpyrrolidinyl)pentane-

25 1,2-dione. A solution of methyl 2-oxo-2-(2-pent-4-enoylpyrrolidinyl) acetate (21.0 g; 88 mmol) in 150 ml THF was cooled to -78°C , under nitrogen, and treated with 200 ml (180 mmol) of 0.9 M 3,3-dimethylpropyl magnesium chloride. After stirring for 2.5 hours, TLC
30 indicated that the reaction was complete. It was quenched with 300 ml of saturated NH_4Cl followed by 200 ml of ethyl acetate. The layers were separated and the aqueous layer was extracted once more with 300 ml of ethyl acetate. The combined organic layers were dried
35 over MgSO_4 , filtered, concentrated, and the product

purified on silica gel with 20% ethyl acetate in hexane, to obtain 3,3-dimethyl-1-(2-pent-4-enoylpyrrolidinyl)pentane-1,2-dione as a light yellow oil, 21.0 g (85%).

5 3,3-Dimethyl-1-[2-(5-(3-pyridyl)pent-4-enoyl)pyrrolidinyl]pentane-1,2-dione. To a solution of olefin 3,3-dimethyl-1-(2-pent-4-enoylpyrrolidinyl)pentane-1,2-dione (500 mg; 1.78 mmol) in 7 ml of Et₃N was added 3-bromopyridine (310 mg; 1.96 mmol), palladium (II) acetate (20 mg; 0.09 mmol), and tri-(orthotolyl) phosphine (108 mg; 0.36 mmol), and the mixture was
10 refluxed overnight. The mixture was concentrated and the products purified on a silica gel column, eluting with a gradient from 50% ethyl acetate in hexane to 75%
15 ethyl acetate. Two products were obtained as light yellow oils. The major product (85% of the mixture) was the product of aryl coupling to the terminus of the C-C double bond, 3,3-dimethyl-1-[2-(5-(3-pyridyl)pent-4-enoyl)pyrrolidinyl]pentane-1,2-dione; the minor product
20 was the product of coupling at the more substituted carbon. The overall yield of the desired product was 480 mg (75%).

3,3-Dimethyl-1-[2-(5-(3-pyridyl)pentanoyl)pyrrolidinyl]pentane-1,2-dione (2). Platinum oxide (12
25 mg) was added to a solution of 3,3-dimethyl-1-[2-(5-(3-pyridyl)pent-4-enoyl)pyrrolidinyl]pentane-1,2-dione (300 mg; 0.84 mmol) in methanol (8 ml). The mixture was hydrogenated at 1 atm. for 2.5 hours. TLC indicated
30 that the reaction was complete, and it was filtered through Celite and concentrated. Eluting through a plug of silica gel (ethyl acetate) furnished analytically pure material, 260 mg (87%). ¹H NMR (CDCl₃, 400 MHz): δ 0.87 (t, 3H, J=7.5); 1.21 (s, 6H); 1.64 (m, 4H); 1.69 (m, 2H); 1.78 (m, 1H); 1.96 (m, 2H); 2.15 (m, 1H); 2.53 (m,
35 1H); 2.63 (m, 2H); 3.49 (m, 1H); 3.53 (m, 1H); 4.57 (dd,

1H, δ =8.8, 4.8); 7.20 (m, 1H); 7.49 (m, 1H, δ =7.8); 8.44 (m, 2H). Anal. Calcd. for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.15; H, 8.54; N, 7.76. TLC: R_f =0.80 (ethyl acetate:ethanol 4:1). Note: this final
 5 hydrogenation step may be done using 10% Pd/C, and hydrogenating for 5 hours at 60 psi. Ethanol or ethyl acetate may be used instead of methanol.

EXAMPLE 5

Synthesis of (2S)-3,3-dimethyl-1-[2-(5-(4-hydroxy-phenyl)pentanoyl)pyrrolidinyl]pentane-1,2-dione (68)

10 The method of Example 4 was utilized to prepare 3,3-dimethyl-1-(2-pent-4-enoylpyrrolidinyl)pentane-1,2-dione.

3,3-Dimethyl-1-(2-[5-[4-(phenylmethoxy)phenyl]pent-4-enoyl]pyrrolidinyl)pentane-1,2-dione. A solution of
 15 3,3-dimethyl-1-(2-pent-4-enoylpyrrolidinyl)pentane-1,2-dione (1.73 g; 6.20 mmol), 4-benzyloxybromobenzene (1.80 g; 6.83 mmol), palladium (II) acetate (70 mg; 0.31 mmol), and tri(orthotolyl)phosphine (380 mg; 1.24 mmol)
 20 in triethylamine (23 ml) was refluxed overnight. The mixture was concentrated in vacuo and purified on a silica gel column, eluting with a gradient from 10% ethyl acetate/hexane to 20% ethyl acetate/hexane, to obtain 1.72 g (60%) of 3,3-dimethyl-1-(2-[5-[4-(phenylmethoxy)phenyl]pent-4-enoyl]pyrrolidinyl)pentane-
 25 1,2-dione as a yellow oil.

1-[2-[5-(4-Hydroxyphenyl)pentanoyl]pyrrolidinyl]-3,3-dimethylpentane-1,2-dione (68). A mixture of 1.63 g (3.53 mmol) of 3,3-dimethyl-1-(2-[5-[4-(phenylmethoxy)phenyl]pent-4-enoyl]pyrrolidinyl)pentane-1,2-dione and
 30 400 mg of 10% Pd/C in 100 ml of ethyl acetate was hydrogenated at 50 psi overnight. The mixture was filtered through Celite, concentrated, and chromatographed (25% ethyl acetate/hexane) to obtain 800
 35 mg (61%) of 1-(2-[5-(4-hydroxyphenyl)pentanoyl]

pyrrolidinyl)-3,3-dimethylpentane-1,2-dione (68). ¹H NMR (CDCl₃, 400 MHz): δ 0.87 (t, 3H, J=7.50); 1.21 (s, 6H); 1.63 (m, 4H); 1.67 (m, 2H); 1.93 (m, 3H); 2.04 (m, 1H); 2.52 (m, 4H); 3.47 (m, 2H); 4.57 (m, 1H); 6.72 (d, 2H, J=8.40); 7.03 (d, 2H, J=8.40). Anal. Calcd. for C₂₂H₃₁NO₄: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.64; H, 8.44; N, 3.65. TLC: R_f=0.45 (25% ethyl acetate/hexane).

EXAMPLE 6

10 Synthesis of 2-phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate (10)

Methyl (2S)-1-(1,2-dioxo-2-methoxyethyl)-2-pyrrolidinecarboxylate. A solution of L-proline methyl ester hydrochloride (3.08 g; 18.60 mmol) in dry methylene chloride was cooled to 0°C and treated with triethylamine (3.92 g; 38.74 mmol; 2.1 eq). After stirring the formed slurry under a nitrogen atmosphere for 15 min, a solution of methyl oxalyl chloride (3.20 g; 26.12 mmol) in methylene chloride (45 ml) was added dropwise. The resulting mixture was stirred at 0°C for 1.5 hour. After filtering to remove solids, the organic phase was washed with water, dried over MgSO₄ and concentrated. The crude residue was purified on a silica gel column, eluting with 50% ethyl acetate in hexane, to obtain 3.52 g (88%) of the product as a reddish oil. Mixture of *cis-trans* amide rotamers; data for *trans* rotamer given. ¹H NMR (CDCl₃): δ 1.93 (dm, 2H); 2.17 (m, 2H); 3.62 (m, 2H); 3.71 (s, 3H); 3.79, 3.84 (s, 3H total); 4.86 (dd, 1H, J=8.4, 3.3).

30 Methyl (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylate. A solution of methyl (2S)-1-(1,2-dioxo-2-methoxyethyl)-2-pyrrolidinecarboxylate (2.35 g; 10.90 mmol) in 30 ml of tetrahydrofuran (THF) was cooled to -78°C and treated with 14.2 ml of a 1.0 M

solution of 1,1-dimethylpropylmagnesium chloride in THF. After stirring the resulting homogeneous mixture at -78°C for three hours, the mixture was poured into saturated ammonium chloride (100 ml) and extracted into ethyl acetate. The organic phase was washed with water, dried, and concentrated, and the crude material obtained upon removal of the solvent was purified on a silica gel column, eluting with 25% ethyl acetate in hexane, to obtain 2.10 g (75%) of the oxamate as a colorless oil, ¹H NMR (CDCl₃): δ 0.88 (t, 3H); 1.22, 1.26 (s, 3H each); 1.75 (dm, 2H); 1.87-2.10 (m, 3H); 2.23 (m, 1H); 3.54 (m, 2H); 3.76 (s, 3H); 4.52 (dm, 1H, J=8.4, 3.4).

(2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidine-carboxylic acid. A mixture of methyl (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylate (2.10 g; 8.23 mmol), 1 N LiOH (15 ml), and methanol (50 ml) was stirred at 0°C for 30 minutes and at room temperature overnight. The mixture was acidified to pH 1 with 1 N HCl, diluted with water, and extracted into 100 ml of methylene chloride. The organic extract was washed with brine and concentrated to deliver 1.73 g (87%) of snow-white solid which did not require further purification, ¹H NMR (CDCl₃): δ 0.87 (t, 3H); 1.22, 1.25 (s, 3H each); 1.77 (dm, 2H); 2.02 (m, 2H); 2.17 (m, 1H); 2.25 (m, 1H); 3.53 (dd, 2H, J=10.4, 7.3); 4.55 (dd, 1H, J=8.6, 4.1).

2-phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate (10). To a solution of (2S)-1-(1,2-dioxo-3,3-dimethylpentyl)-2-pyrrolidinecarboxylic acid (241 mg; 1.0 mmol) in CH₂Cl₂ (10 ml) was added dicyclohexylcarbodiimide (226 mg; 1.1 mmol). After stirring the resulting mixture for 5 minutes, the solution was cooled to 0°C and treated with a solution of phenyl mercaptan (138 mg; 1.0 mmol) and 4-dimethylaminopyridine (6 mg) in 5 ml of CH₂Cl₂. The

mixture was allowed to warm to room temperature with stirring overnight. The solids were removed by filtration and the filtrate was concentrated in vacuo; the crude residue was purified by flash chromatography (10:1 hexane:EtOAc) to obtain 302 mg (84%) of 10 as an oil, ^1H NMR (CDCl_3 , 300 MHz): δ 0.85 (t, 3H, $J=7.5$); 1.29 (s, 3H); 1.31 (s, 3H); 1.70-2.32 (m, 6H); 2.92 (t, 2H, $J=7.4$); 3.22 (t, 2H, $J=7.4$); 3.58 (m, 2H); 4.72 (m, 1H); 7.23-7.34 (m, 5H). Anal. Calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_3\text{S} \cdot 0.4\text{H}_2\text{O}$: C, 65.15; H, 7.60; N, 3.80. Found: C, 65.41; H, 7.49; N, 3.72.

EXAMPLE 7

Synthesis of 2-phenyl-1-ethyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate (9)
Methyl 1-(1,2-dioxo-2-methoxyethyl)-2-piperidine-carboxylate. A solution of methyl pipercolate hydrochloride (8.50 g; 47.31 mmol) in dry methylene chloride (100 ml) was cooled to 0°C and treated with triethylamine (10.5 g; 103 mmol; 2.1 eq). After stirring the formed slurry under a nitrogen atmosphere for 15 minutes, a solution of methyl oxalyl chloride (8.50 g; 69.4 mmol) in methylene chloride (75 ml) was added dropwise. The resulting mixture was stirred at 0°C for 1.5 hours. After filtering to remove solids, the organic phase was washed with water, dried over MgSO_4 and concentrated. The crude residue was purified on a silica gel column, eluting with 50% ethyl acetate in hexane, to obtain 9.34 g (86%) of the product as a reddish oil. Mixture of *cis-trans* amide rotamers; data for *trans* rotamer given. ^1H NMR (CDCl_3): δ 1.22-1.45 (m, 2H); 1.67-1.78 (m, 3H); 2.29 (m, 1H); 3.33 (m, 1H); 3.55 (m, 1H); 3.76 (s, 3H); 3.85, 3.87 (s, 3H total); 4.52 (dd, 1H).

Methyl 1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidine-carboxylate. A solution of methyl 1-(1,2-dioxo-2-methoxyethyl)-2-piperidinecarboxylate (3.80 g; 16.57 mmol) in 75 ml of tetrahydrofuran (THF) was cooled to -78°C and treated with 20.7 ml of a 1.0 M solution of 1,1-dimethyl-propylmagnesium chloride in THF. After stirring the resulting homogeneous mixture at -78°C for three hours, the mixture was poured into saturated ammonium chloride (100 ml) and extracted into ethyl acetate. The organic phase was washed with water, dried, and concentrated, and the crude material obtained upon removal of the solvent was purified on a silica gel column, eluting with 25% ethyl acetate in hexane, to obtain 3.32 g (74%) of the oxamate as a colorless oil, ¹H NMR (CDCl₃): δ 0.88 (t, 3H); 1.21, 1.25 (s, 3H each); 1.35-1.80 (m, 7H); 2.35 (m, 1H); 3.24 (m, 1H); 3.41 (m, 1H); 3.76 (s, 3H); 5.32 (d, 1H).

1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidine-carboxylic acid. A mixture of methyl 1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidinecarboxylate (3.30 g; 12.25 mmol), 1 N LiOH (15 ml), and methanol (60 ml) was stirred at 0°C for 30 minutes and at room temperature overnight. The mixture was acidified to pH 1 with 1 N HCl, diluted with water, and extracted into 100 ml of methylene chloride. The organic extract was washed with brine and concentrated to deliver 2.80 g (87%) of snow-white solid which did not require further purification, ¹H NMR (CDCl₃): δ 0.89 (t, 3H); 1.21, 1.24 (s, 3H each); 1.42-1.85 (m, 7H); 2.35 (m, 1H); 3.22 (d, 1H); 3.42 (m, 1H); 5.31 (d, 1H).

2-phenyl-1-ethyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate (9). To a solution of 1-(1,2-dioxo-3,3-dimethylpentyl)-2-piperidine-carboxylic acid (255 mg; 1.0 mmol) in CH₂Cl₂ (10 ml) was added dicyclohexylcarbodiimide (226 mg; 1.1

mmol). After stirring the resulting mixture for 5 minutes, the solution was cooled to 0°C and treated with a solution of phenyl mercaptan (138 mg; 1.0 mmol) and 4-dimethylaminopyridine (6 mg) in 5 ml of CH₂Cl₂. The mixture was allowed to warm to room temperature with stirring overnight. The solids were removed by filtration and the filtrate was concentrated in vacuo; the crude residue was purified by flash chromatography (10:1 hexane:EtOAc) to obtain 300 mg (80%) of 9 as an oil, ¹H NMR (CDCl₃, 300 MHz): δ 0.94 (t, 3H, J=7.5); 1.27 (s, 3H); 1.30 (s, 3H); 1.34-1.88 (m, 7H); 2.45 (m, 1H); 2.90 (t, 2H, J=7.7); 3.26 (t, 2H, J=7.7); 3.27 (m, 1H); 3.38 (m, 1H); 5.34 (m, 1H); 7.24-7.36 (m, 5H). Anal. Calcd. for C₂₁H₂₉NO₃S: C, 67.17; H, 7.78; N, 3.73. Found: C, 67.02; H, 7.83; N, 3.78.

EXAMPLE 8

A patient is suffering from a condition or disorder requiring stimulation of damaged neurons, promotion of neuronal regeneration, prevention of neurodegeneration, or treatment of a neurological disorder; wherein the neurological disorder is selected from the group consisting of peripheral neuropathy caused by physical injury or disease state, traumatic injury to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorders relating to neurodegeneration; and wherein the neurological disorder relating to neurodegeneration is selected from the group consisting of Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis. (2S)-3,3-dimethyl-1-[2-(5-(3-pyridyl)pyrrolidinyl)]pentane-1,2-dione, 2-(1-Oxo-4-phenyl)-butyl-1-(3,3-dimethyl-1,2-dioxobutyl)pyrrolidine, (2S)-3,3-dimethyl-1-[2-(5-(4-hydroxyphenyl)pentanoyl)pyrrolidinyl]pentane-1,2-dione,

or 2-((1-oxo-6-phenyl)-hexyl) (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)piperidine, or a pharmaceutical composition comprising the same, may be administered to the patient. Protection from or recovery from the effects of the described condition(s) or disorder(s) is expected to occur following treatment.

The compounds of the present invention have an affinity for the FK506 binding protein, particularly FKBP12. The inhibition of the prolyl peptidyl cis-trans isomerase activity of FKBP may be measured as an indicator of this affinity and as a possible indicator of neurotrophic activity.

K_i Test Procedure

Inhibition of the peptidyl-prolyl isomerase (rotamase) activity of the inventive compounds can be evaluated by known methods described in the literature (Harding et al., *Nature*, 1989, 341:758-760; Holt et al. *J. Am. Chem. Soc.*, 115:9923-9938). These values are obtained as apparent K_i's, and are presented for representative compounds in Table IV. The cis-trans isomerization of an alanine-proline bond in a model substrate, N-succinyl-Ala-Ala-Pro-Phe-p-nitroanilide, is monitored spectrophotometrically in a chymotrypsin-coupled assay, which releases para-nitroanilide from the trans form of the substrate. The inhibition of this reaction caused by the addition of different concentrations of inhibitor is determined, and the data is analyzed as a change in first-order rate constant as a function of inhibitor concentration to yield the apparent K_i values.

In a plastic cuvette are added 950 μ l of ice cold assay buffer (25 mM HEPES, pH 7.8, 100 mM NaCl), 10 μ l

of FKBP (2.5 mM in 10 mM Tris-Cl pH 7.5, 100 mM NaCl, 1 mM dithiothreitol), 25 ml of chymotrypsin (50 mg/ml in 1 mM HCl) and 10 ml of test compound at various concentrations in dimethyl sulfoxide. The reaction is initiated by the addition of 5 ml of substrate (succinyl-Ala-Phe-Pro-Phe-para-nitroanilide, 5 mg/ml in 2.35 mM LiCl in trifluoroethanol).

The absorbance at 390 nm versus time is monitored for 90 seconds using a spectrophotometer and the rate constants are determined from the absorbance versus time data files.

The data for these experiments for representative compounds are presented in Table IV under the column "Ki".

The neurotrophic effects of the compounds of the present invention can be demonstrated in cellular biological experiments *in vitro*, as described below.

Chick Dorsal Root Ganglion

Cultures and Neurite Outgrowth

The neurotrophic effects of the FKBP inhibitor compounds were demonstrated by evaluating the ability of the compounds to promote neurite outgrowth in cultured chick sensory neurons from dorsal root ganglia. Dorsal root ganglia were dissected from chick embryos of ten day gestation. Whole ganglion explants were cultured on thin layer Matrigel-coated 12 well plates with Liebovitz L15 plus high glucose media supplemented with 2 mM glutamine and 10% fetal calf serum, and also containing 10 μ M cytosine β -D arabinofuranoside (Ara C) at 37°C in an environment containing 5% CO₂. Twenty-four hours later, the DRGs were treated with various concentrations of nerve growth factor, immunophilin ligands or combinations of NFG plus drugs. Forty-eight hours after drug treatment, the ganglia were visualized under phase

contrast or Hoffman Modulation contrast with a Zeiss Axiovert inverted microscope. Photomicrographs of the explants were made, and neurite outgrowth was quantitated. Neurites longer than the DRG diameter were counted as positive, with total number of neurites quantitated per each experimental condition. Three to four DRGs are cultured per well, and each treatment was performed in duplicate.

Dose-response curves were generated from which ED_{50} values were obtained. The results of these experiments are presented in Table IV under the column "ED50". Representative photomicrographs of untreated (control) sensory neurons and of sensory neurons treated with compound 1 (10 pM, 1 nM, 1 μ M), and related compounds 2-Phenyl-1-ethyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarbothioate (10 pM, 1 nM, 100 nM) and 2-Phenyl-1-ethyl 1-(3,3-dimethyl-1,2-dioxopentyl)-2-piperidinecarbothioate (10 pM, 1 nM, 100 nM) promoting neurite outgrowth in sensory neurons are shown in FIG.'s 1(A-D), 2(A-D), and 3(A-D), respectively.

MPTP Model of Parkinson's Disease

The remarkable neurotrophic and neuroregenerative effects of the present inventive compounds were further demonstrated in an animal model of neurodegenerative disease. MPTP lesioning of dopaminergic neurons in mice was used as an animal model of Parkinson's Disease. Four week old male CD1 white mice were dosed i.p. with 30 mg/kg of MPTP for 5 days. Test compounds (4 mg/kg), or vehicle, were administered s.c. along with the MPTP for 5 days, as well as for an additional 5 days following cessation of MPTP treatment. At 18 days following MPTP treatment, the animals were sacrificed and the striata were dissected and homogenized. Immunostaining was performed on sagittal and coronal

brain sections using anti-tyrosine hydroxylase 1 g to quantitate survival and recovery of dopaminergic neurons. In animals treated with MPTP and vehicle, a substantial loss of functional dopaminergic terminals was observed as compared to non-lesioned animals. Lesioned animals receiving test compounds showed a significant recovery of TH-stained dopaminergic neurons.

The results of these experiments are presented in TABLE IV under the column "% TH recovery". Quantitation for the recovery of TH-positive dopaminergic neurons in the striatum of animals receiving compounds of the invention, including compound 1, and for representative control and lesioned animals not receiving the test drugs, are presented in FIG. 4.

TABLE IV

In Vitro Test Results

	<u>Compound</u>	<u>Ki, nM</u>	<u>ED50, nM</u>	<u>% TH recovery</u>
	1	31	0.4	23
20	2	210	--	--
	3	85	--	--
	9	104	0.5	61
	10	12	0.8	54
	11	299	0.36	53
25	12	442	0.025	--
	14	313	0.9	48
	28	362	--	52
	29	1698	--	--
	30	34	0.9	48
30	31	62	--	--
	32	7	--	56
	33	68	--	--
	34	8.9	0.011	37.32

	35	347	--	--
	36	1226	--	--
	37	366	--	--
	38	28	--	--
5	39	259	--	--
	40	188	--	25
	41	31	--	--
	42	757	--	--
	43	21	--	50
10	44	127	--	28
	45	1334	--	--
	46	55	--	62
	47	33	--	--
	48	6	--	--
15	49	261	--	--
	50	37	--	--
	51	30	--	--
	52	880	--	--
	53	57	--	--
20	54	79	--	--
	55	962	--	--
	56	90	--	--
	57	139	--	--
	58	196	--	--
25	59	82	--	--
	60	163	--	--
	61	68	--	--
	62	306	5	38
	63	177	--	--
30	64	284	--	--
	65	49	--	23

66	457	-	25
67	788	-	--

5 All publications and patents identified above are hereby incorporated by reference.

10 The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.